Guest Editorial

Cardiology's 10 Greatest Discoveries of the 20th Century

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We present a brief summary of the 10 greatest cardiologic developments and discoveries of the 20th century. Described are electrocardiography; preventive cardiology and the Framingham Study; "lipid hypotheses" and atherosclerosis; coronary care units; echocardiography; thrombolytic therapy; cardiac catheterization and coronary angiography; open-heart surgery; automatic implantable cardiac defibrillators; and coronary angioplasty. These topics are the personal choices of the authors. ***(Tex Heart Inst J 2002; 29:164-71)***

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The great success in lowering cardiovascular mortality rates during the last decades of the 20th century are secondary to the extraordinary strides made in the understanding of basic cardiovascular science and in the development of new diagnostic and therapeutic techniques. We describe the 10 most important cardiologic developments and discoveries of the last century. Without these, the cardiology that we practice today would not be possible. The 10 topics were selected on the basis of personal choice.

1. Electrocardiography

During the latter part of 19th century, much research centered around the electrical activity of the heart, although some of the 1st investigators were unaware of the clinical usefulness of recording cardiac electrical activity. As late as 1911, Augustus Waller, who was the pioneer of electrocardiography, said, "I do not imagine that electrocardiography is likely to find any very extensive use in the hospital. It can at most be of rare and occasional use to afford a record of some rare anomaly of cardiac action."[1] However, just 13 years later, the Nobel Prize in Medicine was awarded to Willem Einthoven, who transformed this curious physiologic phenomenon into an indispensable clinical recording device.

Rudolf von Koelliker and Heinrich Müller were the first to discover, in 1856, that the heart generated electricity.[2] The 1st successful recording of electrical rhythm in the human heart seems to have been made by Alexander Muirhead in 1869–70, using a Thomson siphon recorder at St. Bartholomew's Hospital, London. This equipment was originally devised to record signals passing through the transatlantic cable, which had been laid in 1866.[3] Waller performed his work in the development of electrocardiography at St. Mary's Hospital, Paddington, London. He used the Lipmann capillary electrometer to record electrical reactions of the human heart. In 1887, Waller published the 1st report of a recording of cardiac electricity on the body's surface; he called the recording a "cardiograph."[4] Waller presented his paper titled "A preliminary survey of 2,000 electrocardiograms" before the Physiological Society of London in 1917.[5] Among his contributions were the variability of the electrogram, the dipole concept that led to isopotential mapping, and the vector concept.

Einthoven, born in 1860 in Java, Dutch East Indies (now Indonesia), attended the University of Ütrecht Medical School.[2] In 1887, Einthoven was present at the International Congress of Physiology in London, where he observed Waller demonstrating the use of the capillary electrometer to record an "electrograph" of the heart.[6] Einthoven began to explore the use of the capillary electrometer to record minute electrical currents. In 1895, he was able to detect recognizable waves, which he labeled "P, Q, R, S, and T." The limitations of capillary electrometers led Einthoven to devise a string galvanometer to record cardiac electrical activity.[2,3,6,7]

With his new technique, he standardized the tracings and formulated the concept of "Einthoven's triangle" by mathematically relating the 3 leads *(Lead III = Lead II – Lead I).* He described bigeminy, complete heart block, "P mitrale," right and left and ventricular hypertrophy, atrial fibrillation and flutter, the U wave, and examples of various heart diseases.[2,6,7] Johannes Bosscha, one of Einthoven's teachers, suggested using existing telephone lines to link the hospital to Einthoven's physiology laboratory. This idea increased the clinical availability of Einthoven's instrument by enabling electrocardiographic studies to be made in hospitalized patients.[8]

Within 10 years of Einthoven's clinical studies with the string galvanometer, the potential of electrocardiography was realized. Many arrhythmias were recognized, and the associations of T-wave inversion with angina and arteriosclerosis were identified in 1910. The "father of electrocardiography" was honored with the Nobel Prize in Medicine in 1924. His important contributions laid the foundation for the great discoveries of the 20th century and further advances in the field of cardiology.

2. Preventive Cardiology and the Framingham Study

The Framingham Study is one of the most impressive medical works in the 20th century.[9] During the 1st half of the century, there was a steady increase in deaths attributed to heart disease. However, the causes of coronary heart disease were speculative. Investigations comprised descriptive case reports and case-control comparisons of small studies only.[10] With support from the newly created National Heart Institute (now National Heart, Lung, and Blood Institute [NHLBI]), the 1st collection of information from a community cohort was gathered. Between 1948 and 1951, 1,980 men and 2,421 women were enrolled in an observational study in Framingham, Massachusetts. The 1st report of this long-term study, "Factors of risk in the development of coronary heart disease—six-year follow-up experience; the Framingham Study," was published in the *Annals of Internal Medicine* in 1961.[11] The study showed that high blood pressure, smoking, and high cholesterol levels were major factors in heart disease. From this report, the concept of risk factors emerged, and, with further elaboration through the years, the study provided health professionals with multifactorial risk profiles for cardiovascular disease. These profiles assisted in the identification of candidates who might benefit from preventive measures. The Framingham Study provided information crucial to the recognition and management of atherosclerosis, its causes, and its complications. Fifty years' worth of data collected from the residents of Framingham has produced over 1,000 scientific papers; introduced the concepts of biologic, environmental, and behavioral risk factors; identified major risk factors associated with heart disease, stroke, and other diseases; created a revolution in preventive medicine; and forever changed the ways in which the medical community and the general population view the genesis of disease. Of note, the Framingham Study was the 1st major cardiovascular study that included women participants. Not only was the Framingham Study a milestone in the history of cardiology, but it has served as the model for many other longitudinal cohort studies. We remain indebted to those who initiated the study and thus became pioneers in preventive cardiology.

3. "Lipid Hypotheses" and Atherosclerosis

During the 19th century, arteriosclerosis was well recognized, but its etiologic and pathologic significance had not been established. The hypotheses explaining it ranged from disturbed arterial metabolism to adherent blood clots that gradually changed into arteriosclerotic plaques. In 1904, Felix Marchand introduced the term atherosclerosis and suggested that atherosclerosis was responsible for nearly all obstructive processes in the arteries.[12]

In St. Petersburg, Russia, in 1908, A.I. Ignatowski observed a possible relation between cholesterol-rich foods and experimental atherosclerosis.[13] Another sign that cholesterol might be involved in the pathogenesis of atherosclerosis came 2 years later, when Adolf Windaus showed that atheromatous lesions contained 6 times as much free cholesterol as a normal arterial wall and 20 times more esterified cholesterol.[14] Using cholesterol-fed rabbits to produce experimental atherosclerosis, Nikolai Anichkov demonstrated, in 1913, that it was cholesterol alone that caused these atherosclerotic changes in the rabbit initima.[15] He found early lesions, such as fatty streaks, as well as advanced lesions; by standardizing cholesterol feeding, he discovered that the amount of cholesterol uptake was directly proportional to the degree of atherosclerosis severity. William Dock, in an editorial in 1958, likened the significance of this classic work by Anichkov to that of the discovery of the tubercle bacillus by Robert Koch.[16]

During the 1930s, studies of the blood concentration of cholesterol began, but most of the medical community did not comprehend the clinical importance of such studies. In 1950, John Gofman and his associates identified the low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol using the ultracentrifuge technique.[17] In addition, they found that 101 of 104 men with myocardial infarction had elevated LDL molecules—a finding which they had also observed in their cholesterol-fed atherosclerotic rabbits. Gofman's group observed an inverse relationship between HDLs and risk of coronary artery disease. In 1952, Laurence Kinsell and coworkers found that ingestion of plant foods and avoidance of animal fats decreased the blood level of cholesterol.[18] The most important study to identify blood cholesterol level as a risk factor for coronary artery disease was the Framingham Study, which showed that the risk of developing clinically significant coronary artery disease was a continuous curvilinear function of blood cholesterol levels.

During the 1950s and 1960s, many cholesterol-lowering agents were introduced into clinical use, including nicotinic acid, cholestyramine, clofibrate, and plant sterols. In 1961, the American Heart Association began encouraging people to follow a "prudent diet;"[19] and in 1964, Konrad Bloch and Feodor Lynen received the Nobel Prize in Medicine for their work on the metabolism of cholesterol and fatty acids. During the 1970s, Michael Brown and Joseph Goldstein found the LDL receptor and the LDL pathway and shared the 1985 Nobel Prize in Medicine. Another major breakthrough in the pharmacologic management of hypercholesterolemia was the discovery of the statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors). Akira Endo in Japan discovered the earliest statin, compactin, in 1976.[20] In 1985, the NHLBI established the National Cholesterol Education Program to educate both physicians and patients about the importance of treating hypercholesterolemia, and the 1st guidelines were published in 1988.[21] The more that the beneficial effects of lipid-lowering interventions became manifest via large clinical and angiographic trials, the more such interventions were used in clinical practices for the primary and secondary prevention of coronary artery disease.

4. Coronary Care Units

In the early 1960s, the technique of closed-chest cardiopulmonary resuscitation and continuous telemetry monitoring with an alarm system laid the groundwork for coronary care units (CCUs)—specialized intensive care units for patients with acute myocardial infarctions (AMIs). These developments were combined with 2 simple strategies: 1) the clustering of patients with AMIs on a single hospital unit, where necessary equipment and drugs were readily available and where trained personnel could be in continuous attendance; and 2) the training of specialized nurses to recognize and treat arrhythmias rapidly in the absence of a physician.[22] The major objective was to reduce the number of deaths caused by arrhythmias. However, no measures were available to manage overwhelming shock or refractory pulmonary edema resulting from pump failure. Desmond Julian presented the 1st description of the CCU to the British Thoracic Society in July 1961.[23] The next year, Gaston Bauer and Malcolm White started a CCU in a Sydney hospital. Around the same time, K.W.G. Brown in Toronto, Hughes Day in Kansas, and Lawrence Meltzer in Philadelphia began monitoring patients with myocardial infarctions in CCUs.[23] The importance of the specialized care administered in the CCU was realized in 1967 when Thomas Killip and John Kimball published their experience consisting of 250 patients with AMIs who had been treated in the CCU. Compared with other patients who had experienced AMIs, those treated in the CCU had better survival rates in the absence of cardiogenic shock.[24] Other centers reported similar results.[25-27]

From experience gained in the early CCUs, it soon became apparent that arrhythmias were much more common than had previously been suspected. Ventricular extrasystoles were found to be almost universal and generated a lot of interest as "warning" arrhythmias. Bernard Lown and colleagues reported that they found no occurrence of ventricular fibrillation when patients who experienced warning arrhythmias were treated with lidocaine.[27] The development of CCUs coincided with a rapid expansion in the use of transvenous pacing, which was performed in 35% of patients with AMIs at the New York Hospital–Cornell Medical Center in 1967.[25]

Early success in CCUs with resuscitation and with the detection and treatment of arrhythmias focused researchers' attention on left ventricular failure and cardiogenic shock. The Myocardial Infarction Research Units were created in the United States by the NHLBI, and a large program of research was initiated for the investigation of the hemodynamic effects of myocardial infarction. The Swan-Ganz flow-guided catheter was introduced, and its use for invasive monitoring of cardiac hemodynamics became routine in some centers.[23]

5. Echocardiography

The evolution of ultrasonography dates back to 1880, when Pierre and Jacques Curie discovered piezoelectricity.[28] During World War II, the field of sonar ultrasonography advanced rapidly because of its use for detecting submarines. The pioneers of echocardiography were Inge Edler, a cardiologist at Lund University in Sweden, and Hellmuth Hertz, a Swedish physicist.[29] Edler and Hertz borrowed a sonar device from a local shipyard, improved it, and recorded cardiac echoes from Hertz's own heart. With the development of this ultrasonic "reflectoscope," the new field of echocardiography emerged. Edler and Hertz first reported the continuous recording of movements of the heart walls in 1954 and described the use of the ultrasonic cardiogram for mitral valve diseases in 1956.[30] Edler identified several structures on the echocardiogram and made a film that was shown at the

European Congress of Cardiology in 1960. With the development of Doppler echocardiography in the 1960s, the ink-jet printer (another invention by Hertz) was useful in the development of the color Doppler technique. In 1977, Edler and Hertz were joint recipients of the Lasker Prize, which is the American equivalent of the Nobel Prize in Medicine.

In Germany, Sven Effert and his colleagues identified left atrial masses using cardiac ultrasound in 1959.[31] Effert's team visited the United States in the early 1960s, where they met Claude Joyner and discussed the potential of ultrasonography, including the advantages of its nonhazardous nature. At the University of Minnesota, John Reid, an electrical engineer, with John Wild, worked on tissue characterization using ultrasound and developed the 1st clinical ultrasonic scanner. Later, Reid became a member of Joyner's group in Philadelphia where, in 1963, they published the 1st American article on echocardiography.[32] The American achievements in early clinical echocardiography are credited to Harvey Feigenbaum, who led research in the new field of cardiac ultrasonography. In 1968, in Indianapolis, he started the 1st academic course dedicated solely to cardiac ultrasonography, and in 1972, he wrote the 1st book on echocardiography.[33] As this subspecialty gained acceptance and applicability, newer techniques—such as 2-dimensional, transesophageal, and Doppler echocardiography—were introduced.

6. Thrombolytic Therapy

One of the last century's most exciting developments in the field of cardiology was the introduction of thrombolytic therapy for use in patients experiencing AMIs. In 1933, William Tillet and R.L. Garner discovered that Group A β-hemolytic streptococci produced a fibrinolytic substance, which they called streptococcal fibrinolysin.[34] Haskell Milstone, in 1941, suggested that a plasma factor, which he called a "plasma lysing factor," was necessary for streptococcal-mediated fibrinolysis.[35] L. Royal Christensen, a microbiologist, was able to describe the entire mechanism of streptococcal fibrinolysis in 1945. He showed that human plasma contained the precursor of an enzyme system, which he called plasminogen, and that the streptococcal fibrinolysin, which he named streptokinase, was an activator that could convert plasminogen to the proteolytic and fibrinolytic enzyme plasmin.[36,37] Two years later, Christensen made available to Tillet a crudely purified preparation of streptokinase. Sol Sherry, Alan Johnson, and George Hazlehurst soon joined Tillet in performing animal experiments with streptokinase in order to determine its efficacy in the treatment of acute coronary thrombosis.[38] In 1952, Tillet and Johnson reported lysis of experimental thrombi in rabbits' ears with intravenous streptokinase administered through a peripheral vein.[39] Five years later, Sherry's group reported a rational approach to thrombolysis using a loading dose and a sustaining infusion of streptokinase sufficient to increase the clot-dissolving activity of plasma by several hundred-fold and to maintain a plasma streptokinase concentration of about 10 μ/mL.[40]

The 1st study of intravenously administered streptokinase was performed in patients who had AMIs in 1958.[41] The importance of thrombolysis in such patients was highlighted when Marcus DeWood provided angiographic evidence of a very high incidence of total occlusion of infarct-related arteries during the early period of infarction,[42] and Peter Rentrop and his group demonstrated rapid recanalization after local administration of streptokinase directly into an infarct-related artery.[43] Thereafter, the Netherlands trial, the Western Washington trials, and ISIS-2 demonstrated both short- and long-term benefits of thrombolytic therapy.[44-46]

7. Cardiac Catheterization and Coronary Angiography

In 1844, Claude Bernard, a noted French research physiologist, used catheters to record intracardiac pressures in animals and coined the term "cardiac catheterization."[47] With the discovery of x-rays in 1895 by Wilhelm Roentgen, a new approach to the study of cardiac anatomy became possible.[48] Two 2 German physicians, Friedrich Jamin and Hermann Merkel, published the 1st roentgenographic atlas of the human coronary arteries in 1907. In this publication, the authors presented their study of 29 hearts in which the coronary arteries were injected with a suspension of red lead in gelatin.[49] In 1929, a young surgical resident, Werner Forssmann, performed the 1st documented human cardiac catheterization on himself in Eberswald, Germany. He anesthetized his left elbow, inserted a catheter into his antecubital vein, and confirmed the position of the catheter tip in the right atrium by use of radiography. His goal was to find a safe and effective way to inject drugs for cardiac resuscitation.[50] Forssmann soon extended his experiments to include the intracardiac injection of contrast material through a catheter placed in the right atrium. His contributions, along with the development of nontoxic contrast media and the steady advances in radiological techniques, prepared the way for the development of coronary angiography.[51]

André Cournand and Dickinson Richards, in 1941, used the cardiac catheter as a diagnostic tool for the 1st time, applying catheterization techniques to measure right-heart pressures and cardiac output.[47] For their landmark work, they shared a Nobel Prize in Medicine with Forssmann in 1956. In 1958, Mason Sones performed selective coronary arteriography in a series of more than 1,000 patients, and he published a brief description of his technique in *Modern Concepts of Cardiovascular Diseases* 4 years later.[52] This development initiated a period of rapid growth in coronary arteriography during the mid 1960s. Melvin Judkins, a radiologist who had studied coronary angiography with Sones, created his own system of coronary imaging in 1967, introducing a series of specialized catheters and perfecting the transfemoral approach.[53]

8. Open-Heart Surgery

Wilfred Bigelow and his team performed open-heart procedures in animals with the use of hypothermia in 1949.[54] This prompted more research on the applicability of hypothermia in human beings. In 1953, John Lewis performed the 1st successful closure of an atrial septal defect in a 5-year-old girl, using the open-heart hypothermic technique that Bigelow's group had developed.[55] In the decade between the mid-fifties and the mid-sixties, surgical research was very much focused on various techniques of hypothermia and their possible clinical application

The heart-lung machine, which offered additional protection to vital organs, was used by John Gibbon in 1953 during the repair of an atrial septal defect and was a major advance in open-heart surgery.[56] In "Milestones in Chest Surgery," Eloesser wrote, "Gibbon's idea and its elaboration take their place among the boldest and the most successful feats of man's mind."[57] The experience gained with open-heart surgery for congenital lesions enabled surgeons to attempt cardiac valve repair and replacement. In 1956, Walton Lillehei and his team corrected pure mitral regurgitation with suture plication of the commissures under direct vision. After that time, many surgeons around the world became involved in direct vision repair,[58] and prosthetic valves were introduced for cardiac valve replacement.

In 1935, Claude Beck of the Cleveland Clinic published his classic paper, "The development of a new blood supply to the heart by operation," which described his technique of grafting a flap of the pectoralis muscle over the exposed epicardium to create a new blood supply.[59] His work in myocardial revascularization spanned more than 3 decades and captured the imagination of many surgeons. Arthur Vineberg used the internal mammary artery to provide a new source of blood to the myocardium in 1946.[60] This technique became very popular; about 5,000 such operations were performed between 1950 and 1970. In 1964, Vasilii Kolessov, a Russian cardiac surgeon, performed the 1st internal mammary artery–coronary artery anastomosis.[61] René Favaloro achieved a physiologic approach in the surgical management of coronary artery disease—the bypass grafting procedure—at the Cleveland Clinic in May of 1967.[62] He used a saphenous vein autograft to replace a stenotic segment of the right coronary artery. Later that year, he began to use the saphenous vein as a bypassing channel. Soon Dudley Johnson extended the bypass procedure to include the left coronary arterial systems.[63] In 1968, Charles Bailey and Teruo Hirose[64] and George Green[65] used the internal mammary artery instead of the saphenous vein for bypass grafting. Today, coronary artery bypass grafting has become one of the most common operations and is performed all over the world.

9. Automatic Implantable Cardiac Defibrillators

Perhaps the 1st successful attempt at electrical defibrillation occurred in 1775 when Peter Abildgaard, a Danish veterinarian, evaluated the effects of electrical shock and countershock on chickens.[66] In 1899, Jean-Louis Prevost and Frederic Batelli were the first to thoroughly study the effects of electrical discharge on the heart. They noted that if shock was applied within seconds of the onset of fibrillation, the result was defibrillation, which successfully restored sinus rhythm.[67] During the early 1930s, D.R. Hooker and his team refined the existing knowledge about defibrillation.[68]

The original concept of the artificial pacemaker is attributed to Albert Hyman, whose paper on the topic appeared in the *Archives of Internal Medicine* in 1932.[69] Fifteen years later, Beck was the first to apply electrical defibrillation to a human heart in the operating room.[70] Bigelow, John Callaghan, and John Hopps, at the Banting Institute in Toronto, developed a technique of transvenous pacing, which they reported in 1950; Smith and Stone Ltd. built the 1st commercial pacemaker to their design.[71] In 1956, Paul Zoll and coworkers performed the 1st successful external defibrillation in a human subject.[72] In Sweden, Åke Senning and Rune Elmqvist designed a miniature pulse generator, which was implanted after a thoracotomy in 1958.[73] Wilson Greatbatch, in the United States, devised an implantable pacemaker powered by a mercury-zinc battery.[74] The early devices were all asynchronous; the 1st atrioventricular (AV) synchronous pacemaker, which simulated a true physiologic state, was implanted in 1962.[75]

These achievements and the expanding knowledge of clinical electrophysiology led to the invention of the automatic implantable cardiac defibrillator (AICD). This device was meant to abort ventricular fibrillation at its onset, thus averting the inevitably fatal outcome. Michel Mirowski, Morton Mower, and William Staewen at Sinai Hospital of Baltimore collaborated on the AICD in 1969. The next year, they published their animal experiments in the *Archives of Internal Medicine.*[76] The concept of the AICD generated a lot of criticism,[77] but the Baltimore group continued to pursue their research. Marlin Heilman (the founder of Medrad, a small company that supplied angiographic catheters), joined that group in 1972. Heilman helped to make sensing circuits that could identify ventricular fibrillation on the basis of a mathematical formula called the probability density function.[77] In February 1980, after extensive animal research, Mirowski's team successfully treated their 1st human patient with an AICD.[78] In their first 50 patients, the mortality rate was less than 10%. Soon the AICD became the treatment of choice for patients with life-threatening ventricular tachyarrhythmias by consistently outperforming the best medications available for these patients.

10. Coronary Angioplasty

In 1964, Charles Dotter and Melvin Judkins described a new technique for relieving stenosis of the iliofemoral arteries with rigid dilators.[79] Despite the fact that this technique was developed in Oregon, the procedure was largely ignored in the United States because of technical difficulties and complications. Nonetheless, this technique was used to treat large numbers of patients in Europe. In Zurich, Andreas Gruentzig substituted a balloon-tipped catheter for the rigid dilator and performed the 1st peripheral balloon angioplasty in a human being in 1974.[80] After achieving success with coronary angioplasty in animals, Gruentzig and his colleagues performed the 1st intraoperative balloon angioplasty on the human heart. Soon, Gruentzig accomplished the 1st coronary angioplasty in a patient who was awake. On 16 September 1977, Gruentzig performed balloon angioplasty on an isolated stenosis of the proximal left anterior descending coronary artery in a 37-year-old man who had consented to angioplasty even after being informed that he would be the 1st patient so treated.[81] This procedure was followed by a landmark article in the *New England Journal of Medicine* by Gruentzig's team, in which they described their technique of percutaneous transluminal coronary angioplasty (PTCA) as used in 50 patients.[82] The Gruentzig technique took the cardiologic community by storm, and the era of interventional cardiology was born. This extraordinary achievement could not have been accomplished without the previous development of coronary angiography, coronary bypass surgery, and peripheral vascular dilatation. An international registry of PTCA was established to provide a method for systematic evaluation of this new procedure. Even after Gruentzig's untimely death in 1985, his technique continued to evolve and subsequently led to applications such as coronary atherectomy (1986) and coronary stenting (1987). By 1997, angioplasty had become one of the most common medical interventions in the world.

References

1. Barker LF. Electrocardiography and phonocardiography: A collective review. Bull Johns Hopkins Hosp 1910;21:358-89.
2. Burch GE, DePasquale NP. A history of electrocardiography. Chicago: Year Book Medical Publishers; 1964.
3. Burnett J. The origins of the electrocardiograph as a clinical instrument. Med Hist Suppl 1985;5:53-76.
4. Burchell HB. A centennial note on Waller and the first human electrocardiogram. Am J Cardiol 1987;59:979-83.
5. Waller AD. A preliminary survey of 2000 electro cardiograms (Proceedings of the Physiological Society, July 28, 1917). J Physiol 1917;51:xvii-xviii.
6. Fye WB. A history of the origin, evolution, and impact of electrocardiography [published erratum appears in Am J Cardiol 1995;76:64]. Am J Cardiol 1994;73:937-49.
7. Snellen HA. Selected papers on electrocardiography of Willem Einthoven. The Hague (Netherlands): Leiden University Press; 1977.
8. Cooper JK. Electrocardiography 100 years ago. Origins, pioneers, and contributors. N Engl J Med 1986;315:461-4.
9. Brink S. Unlocking the heart's secrets. US News World Rep 1998;125:56-99.
10. Kannel WB. Clinical misconceptions dispelled by epidemiological research. Circulation 1995;92:3350-60.
11. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J 3rd. Factors of risk in the development of coronary heart disease—six-year follow-up experience. The Framingham Study. Ann Intern Med 1961;55:33-50.
12. Marchand F. "Ueber Atherosclerosis," Verhandlungen der Kongresse fur Innere Medizin. 21 Kongresse; 1904.
13. Ignatowski AI. Ueber die Wirkung der tiershen Einwesses auf der Aorta. Virchows Arch Pathol Anat 1909;198:248.
14. Windaus A. Ueber der Gehalt normaler und atheromastoser Aorten an Cholesterol and Cholesterinester. Zeitschrift Physiol Chem 1910;67:174.
15. Anichkov N, Chalatov S. Ueber experimentelle Cholesterinsteatose: Ihre Bedeutung fur die Enstehung einiger pathologischer Proessen. Centrbl Allg Pathol Pathol Anat 1913; 24:1-9.
16. Dock W. Research in arteriosclerosis—the first fifty years [editorial]. Ann Intern Med 1958;49:699-705.
17. Gofman JW, Jones HB, Lindgren FT, Lyon TP, Elliot HA, Strisower B. Blood lipids and human atherosclerosis. Circulation 1950;2:161-78.
18. Kinsell LW, Patridge J, Boling L, Margen S, Michaels G. Dietary modification of serum cholesterol and phospholipid levels [letter]. J Clin Endocrinol 1952;12:909-13.
19. Steinberg D, Gotto AM Jr. Preventing coronary artery disease by lowering cholesterol levels: fifty years from bench to bedside. JAMA 1999;282:2043-50.
20. Endo A. The discovery and development of HMG-CoA inhibitors. J Lipid Res 1992;33:1569-82.
21. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Arch Intern Med 1988;148: 36-69.
22. Braunwald E. Thirty-five years of progress in cardiovascular research. Circulation 1984;70(5 Pt 2):III8-25.
23. Julian DG. The history of coronary care units. Br Heart J 1987;57:497-502.
24. Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol 1967;20:457-64.
25. Meltzer LE. Presbyterian-University of Pennsylvania Medical Center, Philadelphia. In: Julian DG, Oliver MF, edi-

tors. Acute myocardial infarction. Edinburgh: Livingstone; 1968. p. 3-6.
26. Brown KWG, MacMillan RL. The effectiveness of the system of coronary care. In: Meltzer LE, Dunning AJ, editors. Textbook of coronary care. Amsterdam: Excerpta Medica; 1972. p. 52-7.
27. Lown B, Fakhro AM, Hood WB Jr, Thorn GW. The coronary care units. New perspectives and directions. JAMA 1967;199:188-98.
28. Curie P, Curie J. Development, par pression de l'electricite polaire dans les cristaux hemiedres a faces inclines. Comptes Rendus 1880;91:291-5.
29. Edler I, Hertz CH. Use of ultrasonic reflectoscope for the continuous recording of movements of heart walls. Kungl Fysiogr Sallsk Lund Forh 1954;24:40.
30. Edler I. Ultrasound cardiogram in mitral valve disease. Acta Chir Scand 1956;111:230.
31. Effert S, Domanig E. The diagnosis of intraatrial tumor and thrombi by the ultrasonic echo method. Med Meth 1959; 4:1.
32. Joyner CR Jr, Reid JM, Bond JP. Reflected ultrasound in the assessment of mitral valve disease. Circulation 1963;27: 503-11.
33. Feigenbaum H. Evolution of echocardiography. Circulation 1996;93:1321-7.
34. Tillet WS, Garner RL. The fibrinolytic activity of hemolytic streptococci. J Exp Med 1933;58:485-502.
35. Milstone H. A factor in normal human blood which participates in streptococcal fibrinolysis. J Immunol 1941;42: 109-16.
36. Christensen LR. Streptococcal fibrinolysis: a proteolytic reaction due to a serum enzyme activated by streptococcal fibrinolysin. J Gen Physiol 1945;28:363-83.
37. Christensen LR, MacLeod CM. A proteolytic enzyme of the serum: characterization, activation, and reaction with inhibitors. J Gen Physiol 1945;28:559-83.
38. Sherry S. The origin of thrombolytic therapy. J Am Coll Cardiol 1989;14:1085-92.
39. Johnson AJ, Tillet WS. The lysis in rabbits of intravascular blood clots by the streptococcal fibrinolytic system (streptokinase). J Exp Med 1952;95:449-64.
40. Sherry S, Fletcher AP, Alkjaersig N, Smyrniotis FE. An approach to intravascular fibrinolysis in man. Trans Assoc Am Phys 1957;70:288-96.
41. Fletcher AP, Alkjaersig N, Smyrniotis FE, Sherry S. The treatment of patients suffering from early myocardial infarction with massive and prolonged streptokinase therapy. Trans Assoc Am Phys 1958;71:287-96.
42. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980;303:897-902.
43. Rentrop KP, Blanke H, Karsch KR, Wiegand V, Kostering K, Oster H, Leitz K. Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase. Clin Cardiol 1979;2:354-63.
44. Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington Randomized Trial of Intracoronary Streptokinase in Acute Myocardial Infarction. N Engl J Med 1983; 309:1477-82.
45. Simoons ML, Vos J, Tijssen JG, Vermeer F, Verheugt FW, Krauss XH, Cat VM. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of The Netherlands. J Am Coll Cardiol 1989;14:1609-15.
46. Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R. ISIS-2: 10-year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. BMJ 1998;316:1337-43.
47. Mueller RL, Sanborn TA. The history of interventional cardiology: cardiac catheterization, angioplasty, and related interventions. Am Heart J 1995;129:146-72.
48. Fye WB. Coronary arteriography—it took a long time! Circulation 1984;70:781-7.
49. Jamin F, Merkel H. Die koronararterien des menschlichen herzens unter normalen und pathologischen verhaltnissen. Jena: Gustave Fischer; 1907.
50. Forssmann W. Experiments on myself. Memoirs of a surgeon in Germany. New York: St. Martin's Press; 1974.
51. Abrams HL. Angiocardiography and thoracic aortography. In: Bruwer AJ, editor: Classic descriptions in diagnostic roentgenology. Vol 1. Springfield (IL): Charles C. Thomas; 1964. p. 492-501.
52. Sones FM Jr, Shirey EK. Cine coronary arteriography. Mod Concepts Cardiovasc Dis 1962;31:735-8.
53. Information about Melvin Judkins found at ptca.org/archive/bios/judkins.html. Accessed January 2002.
54. Bigelow WG, Lindsay WK, Greenwood WF. Hypothermia: its possible role in cardiac surgery: an investigation of factors governing survival in dogs at low body temperatures. Ann Surg 1950;132:849-66.
55. Lewis FJ, Taufic M. Closure of atrial septal defects with the aid of hypothermia; experimental accomplishments and the report of one successful case. Surgery 1953;33:52-9.
56. Gibbon JH Jr. The development of the heart-lung apparatus. Am J Surg 1978;135:608-19.
57. Eloesser L. Milestones in chest surgery. J Thorac Cardiovasc Surg 1970;60:157-65.
58. Lillehei CW, Gott VL, DeWall RA, Varco RL. The surgical treatment of stenotic or regurgitant lesions of the mitral and aortic valves by direct vision utilizing a pump-oxygenator. J Thorac Surg 1958;35:154-90.
59. Beck CS. The development of a new blood supply to the heart by operation. Ann Surg 1935;102:801-13.
60. Vineberg AM. Development of an anastomosis between the coronary vessels and a transplanted internal mammary artery. Can Med Assoc J 1946;55:117.
61. Kolessov VI. Mammary artery-coronary artery anastomosis as method of treatment for angina pectoris. J Thorac Cardiovasc Surg 1967;54:535-44.
62. Favaloro RG, Effler DB, Cheanvechai C, Quint RA, Sones FM Jr. Acute coronary insufficiency (impending acute myocardial infarction and myocardial infarction): surgical treatment by the saphenous vein graft technique. Am J Cardiol 1971;28:598-607.
63. Johnson WD, Flemma RJ, Lepley D Jr, Ellison EH. Extended treatment of severe coronary artery disease: a total surgical approach. Ann Surg 1969;170:460-70.
64. Bailey CP, Hirose T. Successful internal mammary-coronary arterial anastomosis using a "minivascular" suturing technic. Int Surg 1968;49:416-27.
65. Green GE. Internal mammary artery-to-coronary artery anastomosis. Three-year experience with 165 patients. Ann Thorac Surg 1972;14:260-71.
66. Abildgaard CP. Tentamina electrica in animalibus instituta. Societatis Medicae Havniensis. Collectanea 1775;2:157-61.
67. Prevost JL, Batelli F. La mort par les decharges electriques. I. Conditions physiques. II. Mecanisme de la mort par des decharges electriques isolees. J Physiol Pathol Gen 1899;1:1085-129.

68. Hooker DR, Kouwenhoven WB, Langworthy OR. The effect of alternating electrical currents on the heart. Am J Physiol 1933;103:444-54.
69. Hyman AS. Resuscitation of the stopped heart by intracardial therapy. Arch Intern Med 1932;50:283-305.
70. Beck CS, Pritchard WH, Feil HS. Ventricular fibrillation of long duration abolished by electric shock. J Am Med Assoc 1947;135:985-6.
71. Bigelow WG, Callaghan JC, Hopps JA. General hypothermia for experimental intracardiac surgery. The use of electrophrenic respirations, an artificial pacemaker for cardiac standstill and the radio-frequency rewarming in general hypothermia. Ann Surg 1950;132:531-9.
72. Zoll P, Paul MH, Linenthal AJ, Norman LR, Gibson W. The effects of external electric currents on the heart. Control of cardiac rhythm and induction and termination of cardiac arrhythmias. Circulation 1956;14:745-56.
73. Elmqvist R. Review of early pacemaker development. Pacing Clin Electrophysiol 1978;1:535-6.
74. Chardack WM, Gage AA, Greatbatch W. A transistorized, self-contained, implantable pacemaker for the long-term correction of complete heart block. Surgery 1960;48:643-54.
75. Nathan DA, Center S, Wu CY. An implantable, synchronous pacemaker for the long-term correction of complete heart block. Circulation 1963;27:682-5.
76. Mirowski M, Mower MM, Staewen WS, Tabatznik B, Mendeloff AI. Standby automatic defibrillator. An approach to prevention of sudden coronary death. Arch Intern Med 1970;126:158-61.
77. Kastor JA. Michel Mirowski and the automatic implantable defibrillator. Am J Cardiol 1989;63:977-82.
78. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med 1980;303:322-4.
79. Dotter CT, Judkins MP. Transluminal treatment of arteriosclerotic obstruction: description of a new technic and a preliminary report of its application. Circulation 1964;30:654-70.
80. Gruntzig A, Kumpe DA. Technique of percutaneous transluminal angioplasty with the Gruntzig balloon catheter. AJR Am J Roentgenol 1979;132:547-52.
81. Hurst JW. The first coronary angioplasty as described by Andreas Gruentzig. Am J Cardiol 1986;57:185-6.
82. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979;301:61-8.